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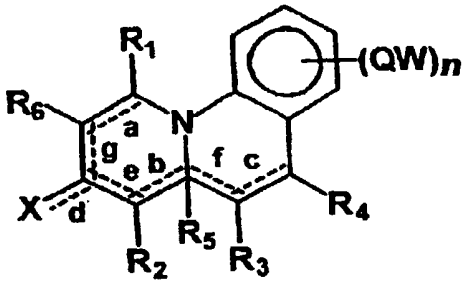
(54) Title: USE OF BENZO[C]QUINOLIZINE DERIVATIVES AS PLANT GROWTH REGULATORS

(57) Abstract

Described herein is the use of benzo[c]quinolizine derivatives of formula (I) as regulators of the growth of plants, and compositions for agricultural use containing the said derivatives or their salts.



(I)

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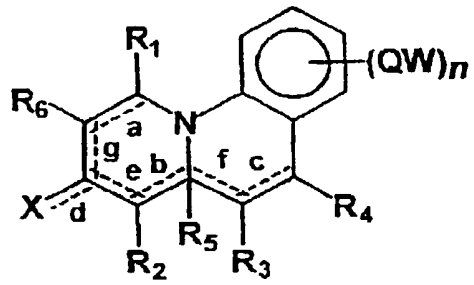
USE OF BENZO[C]QUINOLIZINE DERIVATIVES AS PLANT GROWTH REGULATORS

Scope of invention

The present invention regards the use of benzo[c]quinolizine derivatives of general formula (I)



(I)

in which:

R_1, R_2, R_3, R_4, and R_6, which are the same or different from one another, are chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6} cyclo-alkyl, aryl, heterocycle, halogen, CN, hazide, NRR', C_{1-8} alkylamine, arylamine, C_{1-8} alkyloxy, aryloxy, COOR, and CONRR', where R and R', which are the same or different from one another, are chosen in the group consisting of H, C_{1-8} alkyl, cyclo-alkyl, aryl, heterocycle, and aryl-C_{1-8} alkyl;

R_5 is chosen in the group consisting of H, C_{1-8} alkyl, aryl-C_{1-8} alkyl, COOR, CN, aryl, heterocycle, and the C_{1-8} alkyl heterocycle;

X is chosen in the group consisting of O, C(=O)R, COOR, NO_2, and CONNR', in which R and R' are as defined above;

Q is chosen in the group consisting of: single-bond, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cyclo-alkyl, CO, CONR, and NR, where R is as defined previously;

W is chosen in the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cyclo-alkyl, trifluoromethyl, C_{1-8} alkoxy, C_{1-8} alkoxy-C_{1-8} alkyl, aryl-C_{1-8} alkyl, aryl, aryloxy, arylamine, C_{1-8} alkyl-carbonyl, arylcarbonyl, halogen, CN, NRR', C_{1-8} alkylamine, and heterocycle, in which the alkyl, alkenyl, alkynyl, cyclo-alkyl, aryl, and heterocycle groups may be substituted;

n is 1, 2, 3 or 4;

the mark ---- indicates that the respective bonds a, b, c, d, e, f, and g may be single or double bonds, considering that when b or f are a double bond, the R_5 group is absent,

as regulators of the growth of plants.

State of the art

It is known that steroidal enzymes have a considerable importance both in the field of medicine and in that of sciences related to the development of agriculture and foodstuffs. However, whilst the physiological role of steroids in man has been amply studied and documented, the physiological role of steroids in the vegetable world is less well known.

The growth of plants is governed by complex interactions between environmental signals and internal factors. Light regulates many processes of development throughout the life cycles of the plant, starting from seed germination right up to flower development (J. Chory, Trends, Genet., 1993, 9, 167). In the presence of light, the growth of hypocotyledons is inhibited, cotyledons expand, leaves develop, chloroplasts differentiate producing chlorophyll, and a large number of light-inducible genes are activated.

It has been recently suggested that brassinosteroids, which are the most widespread steroids in higher plants, may be directly involved in the response of plants to light (Chory *et al.*, Proc. Natl. Acad. Sci. 1996, 93, 12066). However, the interactions between phototransduction and hormones are not yet well known. Brassinolid is the steroid that has a fundamental role in the development of plants under the effect of light and has been identified in the larger part of higher plants. It is generated through a metabolic cascade in which campesterol (a compound similar to cholesterol) is reduced to campestanol. The enzyme which is responsible for this reduction is a 5-alpha-reductase steroidal enzyme, named DET2 after the gene of the same name isolated for the plant *Arabidopsis*, which presents a sequence analogy of up to 80% on the conservative amino acids of the iso-enzymes 1 and 2 of the 5-alpha-reductase of humans and rats.

The genetic mutations that inactivate DET2 do not allow production of brassinolid and determine deep alterations in the development of seeds and in *Arabidopsis* plants in the dark or under the effect of light.

In the dark, the plants mutated genetically in DET2 present short and thick hypocotyledons, accumulate anthocyanins, have open and expanded cotyledons, and develop primary-leaf buds. In the light, the mutated plants are smaller and of a darker green, have a reduced apical dominance and male fertility. In addition, they have different responses to light, with delayed flowering and delayed ageing of leaves and chlorophyll (J. Li *et al.*, Science, 1996, 272, 398).

These alterations of the mutating species are reversed with the exogenous addition of brassinolid to the growth medium (J. Li *et al.*, Proc. Natl. Acad. Sci., 1997, 94, 3554-3559).

Detailed description of the invention

It has now been surprisingly found that the products of formula (I) as described above exert an inhibiting action on the 5-alpha-reductase steroidal enzymes, in particular on the DET2 enzyme, and hence are able to affect selectively the growth of plants in the dark and in the light, and can therefore be used as phytopharmaceutical substances in the field of agriculture and foodstuffs both as substances capable of improving the morphogenesis and development of plants that are commercially useful and as potential herbicides that inhibit the development of weeds.

In the products of formula (I) according to the present invention, by C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl group are meant alkyl radicals, either linear or branched, such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propyne, butyne, etc.

By the term cyclo-alkyl the following are meant: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclo-octane, norbornane, camphane, and adamantane.

By the term aryl the following are meant: phenyl and naphthyl.

By the term heterocycle the following are meant in particular: saturated or aromatic heterocycles containing one or more nitrogen atoms, and more in particular, pyridine, imidazole, pyrrole, indole, triazoles, pryrrolidine, and piperidine.

By halogen the following are meant: fluorine, chlorine, bromine, and iodine.

The substituents of the aforementioned W groups are preferably: halogen, OR, phenyl, NRR', CN, COOR, CONRR', and C_{1-8} alkyl (in which R and R' are as defined above).

In particular, according to the present invention the products of formula (I) are preferred in which:

R_5 = H, heterocycle, aryl-C_{1-8} alkyl, or C_{1-8} alkyl heterocycle;

X = 0;

Q = single-bond, CO, CONR, or NR (where R is as defined above);

W = H, F, Cl, Br, Me, *tert*-butyl, C_{1-8} alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8} alkyl, C_{1-8} alkylcarbonyl, or phenylcarbonyl;

n = 1 or 2;

R_1, R_2, R_3, R_4, R_6 = H, Me, CN, phenyl, COOR, or CONRR' (where R and R' are as defined above).

Products preferred according to the present invention are:

1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-8-methyl(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizin-3-one;

1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

4-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

1-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

4a-benzyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-4a-benzyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

5,6-dihydro-(11H)benzo[c]quinolizin-3-one;

8-chloro-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

(*cis*) and (*trans*) 4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;
8-chloro-4-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]
quinolizin-3-one;
4,8-dimethyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;
(*cis*) and (*trans*) 4,8-dimethyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;
(*cis*) and (*trans*) 8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one.

The products of formula (I) may be prepared according to known techniques. The products, and the processes for their preparation, are in any case described in the parallel Patent Application No. PCT/EP97/00552.

For this purpose, a number of products of formula (I) were tested as regards their capacity for modifying seed germination.

The introduction of compounds of formula (I) in various concentrations into the culture medium notably modified germination of *Arabidopsis Thaliana* Columbia (Col 0) seeds, kept in the dark for 10 days, as compared to the germination of non-treated seeds.

The effects observed on the treated seeds (i.e., lower growth of the hypocotyledons, development of cotyledons, and budding of the primary leaves) were similar to those described for seeds of plants genetically mutated as regards the DET2 enzyme, this indicating that the compounds of formula (I) are effective inhibitors in regard to this enzyme.

This observation indicates that the compounds of formula (I), in so far as they are inhibitors of the 5-alpha-reductases, and in particular of DET2 in plants, may be used to modify the germination of the seeds in the dark (if applied on the seeds) and modify the growth of the plants in the light (if applied on the plants). The possible industrial applications may thus regard the increase in germination of seeds of plants useful in agriculture and/or the reduction in the growth of harmful plants.

Example

Batches of 25 seeds of *Arabidopsis Thaliana* Columbia (Col 0) were made to germinate in a suitable culture medium consisting of 0.5 x MS at pH 5.7, containing 1% sucrose, 1x Vitamin B5 Gamborg, and 0.8% phyto-agar in the

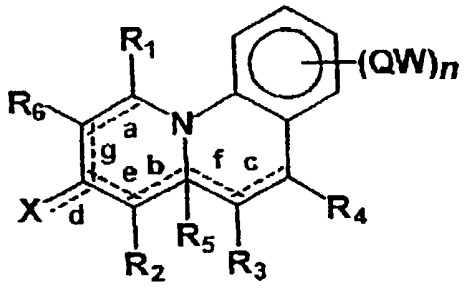
presence of the 1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one inhibitor at the concentrations of 0, 0.01, 0.1, 1 and 10 micromolar. After two hours of treatment in light, the seeds were covered with three layers of aluminium foil and kept at 21°C in a growth chamber. After 10 days in the dark, the length of the hypocotyledons was measured. In the plants not treated with the inhibitor, the length measured was approximately 15-16 mm, whereas in the treated plants the hypocotyledons were progressively shorter as the concentration of inhibitor used was increased.

A reduction of 50% in the hypocotyledons as compared to the controls was found for the seeds treated with a concentration of 0.1 micromolar of inhibitor.

This indicates that the inhibitor at that concentration determines a control over germination of seeds in the dark.

CLAIMS

1. Use of benzo[c]quinolizine compounds of general formula (I)



(I)

in which:

R_1, R_2, R_3, R_4, and R_6, which are the same or different from one another, are chosen in the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6} cyclo-alkyl, aryl, heterocycle, halogen, CN, hazide, NRR', C_{1-8} alkylamine, arylamine, C_{1-8} alkyloxy, aryloxy, COOR, and CONRR', where R and R', which are the same or different from one another, are chosen in the group consisting of H, C_{1-8} alkyl, aryl, heterocycle, aryl-C_{1-8} alkyl, and cyclo-alkyl;

R_5 is chosen in the group consisting of H, C_{1-8} alkyl, aryl-C_{1-8} alkyl, COOR, CN, aryl, heterocycle, and the C_{1-8} alkyl heterocycle;

X is chosen in the group consisting of O, C(=O)R, COOR, NO_2, and CONNR', in which R and R' are as defined above;

Q is chosen in the group consisting of single-bond, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cyclo-alkyl, CO, CONR, and NR, where R is as defined previously;

W is chosen in the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cyclo-alkyl, trifluoromethyl, C_{1-8} alkoxy, C_{1-8} alkoxy-C_{1-8} alkyl, aryl-C_{1-8} alkyl, aryl, aryloxy, arylamine, C_{1-8} alkyl-carbonyl, arylcarbonyl, halogen, CN, NRR', C_{1-8} alkylamine, and heterocycle, in which the alkyl, alkenyl, alkynyl, cyclo-alkyl, aryl, and heterocycle groups may be substituted;

n is 1, 2, 3 or 4;

the mark ⎓ indicates that the respective bonds a, b, c, d, e, f, and g may be single or double bonds, considering that when b or f are a double bond, the R_5 group is absent; (or salts thereof),

as regulators of the growth of plants.

2. Use according to Claim 1, in which the inhibited 5-alpha-reductase steroidal enzyme is DET2.

3. Use according to Claims 1 and 2, in which in the products of formula (I):

R_5 = H or heterocycle;

X = 0;

Q = single-bond, CO, CONR, or NR (where R is as defined above);

W = H, F, Cl, Br, Me, *tert*-butyl, C_{1-8} alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8} alkyl, C_{1-8} alkylcarbonyl, or phenylcarbonyl;

n = 1 or 2;

R_1, R_2, R_3, R_4, R_6 = H, Me, CN, phenyl, COOR, or CONRR' (where R and R' are as defined above).

4. Use according to Claim 3, in which the products of formula (I) are:

1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-8-methyl(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizin-3-one;

1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizin-3-one;

1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

4-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

1-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

5,6-dihydro-(11H)benzo[c]quinolizin-3-one;

8-chloro-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

(*cis*) and (*trans*) 4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-4-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]
quinolizin-3-one;

4,8-dimethyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

(*cis*) and (*trans*) 4,8-dimethyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

(*cis*) and (*trans*) 8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one.

5. Compounds of formula (I) as defined in Claim 1, in which:

R_5 = C_{1-8}-alkyl-aryl or C_{1-8} alkyl heterocycle, and the other substituents are as defined in Claim 1.

6. Compounds according to Claim 5 of formula:

4a-benzyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one;

8-chloro-4a-benzyl-4,4a,5,6-tetrahydro-(11H)-benzo[c] quinolizin-3-one.

7. Composition for regulating the growth of plants, containing as active principle a product of formula (I) according to Claim 1 or mixtures of such products, possibly in combination with additives commonly used in agriculture for this type of preparations.

8. Process for regulating the growth of plants in which on the seeds and/or on the plants an effective quantity of a composition according to Claim 7 is distributed.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 98/04737

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01N43/90 C07D455/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A01N C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 97 29107 A (APPLIED RESEARCH SYSTEMS ;GUARNA ANTONIO (IT); SERIO MARIO (IT)) 14 August 1997 cited in the application see the whole document ---	1-8
Y	CHEMICAL ABSTRACTS, vol. 126, no. 25, 23 June 1997 Columbus, Ohio, US; abstract no. 327248, J.LI ET AL.: "Conservation of function between mammalian and plant steroid 5.alpha.-reductases" XP002086370 see abstract & PROC. NATL. ACAD. SCI. U.S.A., vol. 94, no. 8, 1997, pages 3554-3559, --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1998	14/12/1998

Name and mailing address of the ISA	Authorized officer
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Inte onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 124, no. 23, 3 June 1996 Columbus, Ohio, US; abstract no. 309107, J.LI ET AL.: "A role for brassinosteroids in light-dependent development of Arabidopsis" XP002086371 see abstract & SCIENCE, vol. 272, no. 5260, 1996, pages 398-401, ---	1-8
Y	DATABASE WPI Section Ch, Week 9519 Derwent Publications Ltd., London, GB; Class C03, AN 95-144764 XP002086372 & JP 07 069987 A (SANKYO CO LTD) , 14 March 1995 see abstract ---	1-8
X	R.M.ACHESON ET AL.: "Addition Reactions of Heterocyclic Compounds. Part XLV. New Azepines from Substituted 2-Methylquinolines and Dialkyl Acetylenedicarboxylates" JOURNAL OF THE CHEMICAL SOCIETY, SECTION C: ORGANIC CHEMISTRY., no. 19, 1971, pages 3291-3296, XP002086369 LETCHWORTH GB see page 3296, column 2, paragraph 2 -----	5

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Information on patent family members

Intr ional Application No
PCT/EP 98/04737

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